**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of: **Richard E. Riman, Wojciech Suchanek, Pavel Shuk**

Application No.: **09/800,127** Examiner:

Filed: **March 6, 2001** Group Art Unit: 1614

For: **Magnesium-Substituted Hydroxapatites**

Attorney Docket No.: **P24,186 USA**

**CERTIFICATE OF MAILING**

I hereby certify that this correspondence along with any papers indicated as being enclosed is being deposited with the U.S. Postal Service via First Class Mail addressed to Commissioner for Patents, Washington, D.C. 20231 on 2/5/2003.

Dated: 2/5/2003

Ariel Mellman

Commissioner for Patents
Washington, D.C. 20231

**DECLARATION OF WOJCIECH SUCHANEK, Ph.D.**
**PURSUANT TO 37 C.F.R. § 1.132**

Wojciech Suchanek, Ph.D. declares and states as follows:

1. I am co-inventor of the subject matter that is disclosed and claimed in the subject application. I hold a Ph.D. in Materials Science from the Tokyo Institute of Technology, which I received in September 1996. The title of my thesis was "Hydroxyapatite Ceramics Toughened with Hydroxyapatite Whiskers and Other Additives." The research that served as the basis of the subject application was performed while I was a Research Associate from March 1999 until February 2001 at Rutgers University's Department of Ceramic and Materials Engineering in Piscataway, NJ. I am presently employed as a Research Scientist for Sawyer Research Products, Inc. in Eastlake, Ohio where I am conducting basic research and process improvement on hydrothermal processes. I am experienced and familiar with the subject matter of this patent application.

2. I am also familiar with the prosecution history of this application. The Examiner's position, as I understand it, is that our broadest method claim and certain dependent claims are anticipated by the Dolci et al. published PCT application, WO 00/03747 because at pages

12 and 15 the substitution of magnesium for calcium in hydroxyapatite is shown, with the method by which this is accomplished being shown at page 21. It is my understanding that it is also the Examiner's position that all of the method claims are obvious in view of two United States patents Jarcho, U.S. Patent No. 4,097,935 in view of Ducheyne et al., U.S. Patent No. 5,830,480. As I understand it, the Examiner considered column 5, lines 8-16 of Jarcho to disclose the preparation of our crystalline, phase-pure hydroxyapatite by a mechanochemical process using the diammonium phosphate disclosed at column 8, lines 6-23. The Examiner acknowledged that the replacement of calcium with magnesium in the lattice structure was not disclosed, but cited Ducheyne et al. as disclosing this by using a sol-gel aqueous treatment (columns 2 and 4). It is my understanding that the Examiner considers our process as it is presently claimed to be the obvious use of the magnesium ions of Ducheyne et al. in the process of Jarcho. Finally, it is also my understanding that the Examiner considers the claim limitation "mechanochemically reacting" to be unclear.

3. Regarding the meaning of the claim limitation "mechanochemically reacting," this is well-understood by those of ordinary skill in the art. In addition to books and review articles, hundreds of papers have been published on the subject of mechanochemistry and the mechanochemical processing of materials. I performed a search on the Science Citation Index Database compiled by the Institute for Scientific Information using the keywords "mechanochemistry" and "mechanochemical" and retrieved 1,158 scientific articles published between 1980 and October 2002 in widely accessible journals.

4. Books published on the subject include Avvakumov et al., Soft Mechanochemical Synthesis: A Basis for New Chemical Technologies (Kluwer Academic Publishers, Boston, 2001) and Gutman, Mechanochemistry of Materials (Cambridge International Publishing, Cambridge, UK, 1997). To illustrate that the meaning of the limitation "mechanochemically reacting" is well-known and widely accepted, I am enclosing as Exhibit A a copy of Chapter 4 of Avvakumov et al., as well as copies of the following journal articles:

Boldyrev, "Mechanochemistry and Mechanical Activation of Solids," Solid State Ionics, 63-65, 537-543 (1993); and

McCormick et al., "The Fundamentals of Mechanochemical Processing," JOM, 61-65 (November 1998).

These articles all serve as evidence of the limitation intended by "mechanochemically reacting,"

5. Regarding Dolci et al., page 15 discusses the replacement of some calcium ions with magnesium ions in hydroxyapatite but not by the method that is presently claimed. While pages 13 and 15 disclose sources of calcium ions, phosphate ions and hydroxide ions for use in making a hydroxyapatite, there is no disclosure regarding the addition of magnesium ions to replace calcium ions in the hydroxyapatite lattice structure. The inventors neither demonstrate the synthesis of magnesium-containing hydroxy apatite by the presently claimed hybrid mechanochemical-hydrothermal method, nor do they provide any examples documenting the actual substitution of magnesium for calcium in the hydroxyapatite structure.

6. On page 18 the inventors only mention, "the nanostructured apatites according to the invention may be produced by any several known methods, already in use for the production of nanocrystalline materials." This statement is followed by a general description of synthesis methods, including, at pages 19-20, a "mechanical attrition" method that is essentially a mechanochemical procedure. However, (1) no details are given regarding the synthesis conditions; (2) the method was used to synthesize carbonated apatites, which were subsequently used in comparative tests in examples 1 and 2; the method was not used to make magnesium containing hydroxyapatite; (3) no mention is made of using an aqueous solution as a reaction environment; at page 20, lines 28-30, only air, inert gas, vacuum or liquids such as alcohols, ethers, oils and other organic molecules are disclosed; (4) at page 15, lines 12-19, the inventors clearly state that in an aqueous environment $Mg^{2+}$ ions inhibit the formation of hydroxyapatite and promote the formation of β-tricalcium phosphate (TCP).

7. The disclosure regarding TCP formation is significant. Dolci et al. disclosed that with 10% magnesium, mixtures of hydroxyapatite and TCP are formed, and at 25% magnesium only TCP forms. This disclosure is followed by the statement at lines 20-21 that

magnesium content in biological apatites is very low, about 1%. In other words, Dolci et al. are teaching that what we are doing cannot be done, that hydroxyapatite with magnesium substituted for calcium in the lattice structure cannot be prepared in aqueous environments.

8. In other words, anybody skilled in the art would be informed by Dolci et al. that the replacement of calcium with magnesium in the hydroxyapatite lattice structure to the levels claimed in our patent application cannot be achieved from aqueous solution. Furthermore, while Dolci et al. describe a mechano-chemical method to obtain carbonated hydroxyapatite, disclosed method does not use aqueous solutions. The use of an aqueous solution with at least one reagent soluble in water is the critical feature of our invention that, when used in a hybrid mechanochemical-hydro-thermal process results in the substitution of magnesium for calcium in the hydroxyapatite lattice structure at levels that have not been heretofore achieved.

9. Regarding the Jarcho patent, this has nothing to do with the mechanochemical synthesis of hydroxyapatite. Thus, while even the Examiner acknowledges the substitution of magnesium for calcium is not shown, even if magnesium were included among the reagents it would most likely not replace the calcium in the hydroxyapatite lattice structure to the levels claimed in our patent application under the condition that Jarcho describes. Jarcho himself clearly states in column 17 (lines 42-51) that "[...] addition of a small amount of magnesium ion to the calcium ion prior to reaction of the latter with phosphate ion will favor the formation of whitlockite thereby ultimately affording a whitlockite-enriched biphasic ceramic [...]", which is in an agreement with common knowledge on the effects of Mg on precipitation of calcium phosphates from aqueous solutions (see also Para 14 of this Declaration).

10. In particular, the Jarcho patent describes a process at column 8 in which a calcium phosphate precipitates after being only stirred at room temperature for at least 24 hours and not milled or ground. This is in contrast to the method of the present invention in which high-energy milling equipment is necessary for performance of the mechanochemical-hydro-thermal process step. The well-known need to use such equipment in a mechano-chemical process is disclosed in chapter 4 of the above-mentioned Soft Mechanochemical Synthesis: A Basis for New Chemical Technologies, a copy of which is enclosed.

11. The room temperature process described by Jarcho is also widely used in the world and documented in the scientific literature. As an example, I am enclosing as Exhibit B a copy of a journal article that I co-authored, Suchanek et al., "Processing Properties of Hydroxyapatite-Based Biomaterials for Use as Hard Tissue Replacement Implants," J.Mater. Res., 13(1), 94-117 (1998). This process is known to produce amorphous calcium phosphate (see, for example, LeGeros, Calcium Phosphates in Oral Biology and Medicine (Karger AG, Basel, Switzerland, 1991) 8-9 and Elliott, Structure and Chemistry of the Apatites and other Calcium Orthophosphates (Elsevier, 1994) 53-55, copies of which are enclosed as Exhibits C and D respectively) or hydroxyapatite with a very low crystallinity (see, for example, Ioku et al., Nippon Kagaku Kaishi, 9, 1565-1570 (1988), particularly the Figure 2(A) x-ray diffraction pattern, a copy of which is also enclosed as Exhibit E), that is often strongly non-stoichiometric (see in Exhibits C and D pages 18-21 in Calcium Phosphates in Oral Biology and Medicine and pages 118-127 in Structure and Chemistry of the Apatites and other Calcium Orthophosphates, respectively).

12. Such precipitates differ significantly from the hydroxyapatites synthesized by the hybrid mechanochemical-hydrothermal method of the invention, which exhibit high crystallinity and stoichiometry as demonstrated in several references (Shuk et al., "Mechano-chemical-Hydrothermal Preparation of Crystalline Hydroxyapatite Powder at Room Temperature," J. Mater. Res., 16 (5), 1231-1234 (2001) and Suchanek et al., "Mechanochemical-Hydrothermal Synthesis of Carbonated Apatite Powders at Room Temperature," Biomater., 23 (3), 699-710 (2002) (enclosed as Exhibits F and G). The high crystallinity and stoichiometry is attributable to the unique processing features of our claimed hybrid mechanochemical-hydrothermal process, which is not disclosed by Jarcho.

13. Turning to the Ducheyne et al. patent, this indeed mentions the presence of magnesium ion in the solution during precipitation of the calcium-phosphate phases on the glass surface. In most cases, however, Ducheyne et al. do not specify which calcium phosphate is formed. This is understandable to those skilled in the art, because the films are difficult to characterize and various calcium phosphate phases could form. In Example 4 of Ducheyne et al., the presence of carbonate-hydroxyapatite is inferred from FTIR based upon

P-O vibrations located at 560 and 604 $cm^{-1}$ and the C-O band at 807 $cm^{-1}$. This is an over-statement. Carbonate-hydroxyapatite is just one of the possible phases that exhibit these FTIR vibrations (see, Exhibit C, Calcium Phosphates in Oral Biology and Medicine at page 33). Octacalcium phosphate has a P-O vibration in the same positions, and there is a $HPO_4^{2-}$ derived band overlapping with the C-O band around 870 $cm^{-1}$. In other words, to those skilled in the art, the Ducheyne et al. patent discloses no clear evidence of pure hydroxyapatite phase formation. Why then would one assume that the magnesium ions disclosed therein could be used in the Jarcho process to obtain hydroxyapatite in which magnesium ions are substituted for calcium ions in the lattice structure?

14. Ducheyne et al. do not disclose evidence of any magnesium substitution for calcium in the calcium phosphate layers that are formed. Furthermore, the effect of magnesium upon the precipitation of various calcium phosphates from aqueous solutions is widely accepted and common knowledge among those skilled in the art. (see, for example, Exhibits C and D, Calcium Phosphates in Oral Biology and Medicine at pages 79-80 and 97-99, and Structure and Chemistry of the Apatites and Other Calcium Orthophosphates at pages 44-45 and 53-54, respectively). That is, it is common knowledge that under the experimental conditions described by Ducheyne et al., the presence of magnesium ions in the solutions stabilizes either the amorphous calcium phosphate phase or the whitlockite phase, or, even if hydroxyapatite is formed (for which there is no clear evidence), the level of magnesium substitution is extremely small, about 0.4 weight percent. In other words, the Ducheyne et al. patent neither teaches nor implies how to employ magnesium ions in the process of Jarcho to achieve magnesium substitution for calcium in the hydroxyapatite lattice at the levels obtained by the presently claimed method. To my knowledge, no process capable of doing so has ever been reported that others have been able to successfully reproduce.

15. The presently claimed method is simply not the use of the magnesium-containing calcium-phosphate "solutions" of Ducheyne et al. in the process of Jarcho.

16. I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true and further that the

statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the U.S. Code and that such willful false statements may jeopardize the validity of the application or any patent that issues thereon.

Dated: 1/19/2003

Wojciech Suchanek

Wojciech Suchanek, Ph.D.

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